

# A multiplicative-regression model to compare the risk factors associated with time to graft failure between a first and second renal transplant

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## INTRODUCTION

- ▶ The prognosis of **second kidney transplant recipients (STR)** compared to **first kidney transplant recipients (FTR)** has been frequently studied.
- ▶ But no study has addressed the issue of **comparing the risk factors** associated with the time to graft failure between both groups.
- ▶ The limits of classical survival models:
  - ▶ A comparison of risk factors between both groups is possible but would imply testing interactions of all the factors with the graft rank.
  - ▶ STR-specific covariates (survival time of first transplant, time in dialysis before retransplantation or transplantectomy) cannot be analyzed, despite the knowledge that their use would improve risk evaluation.

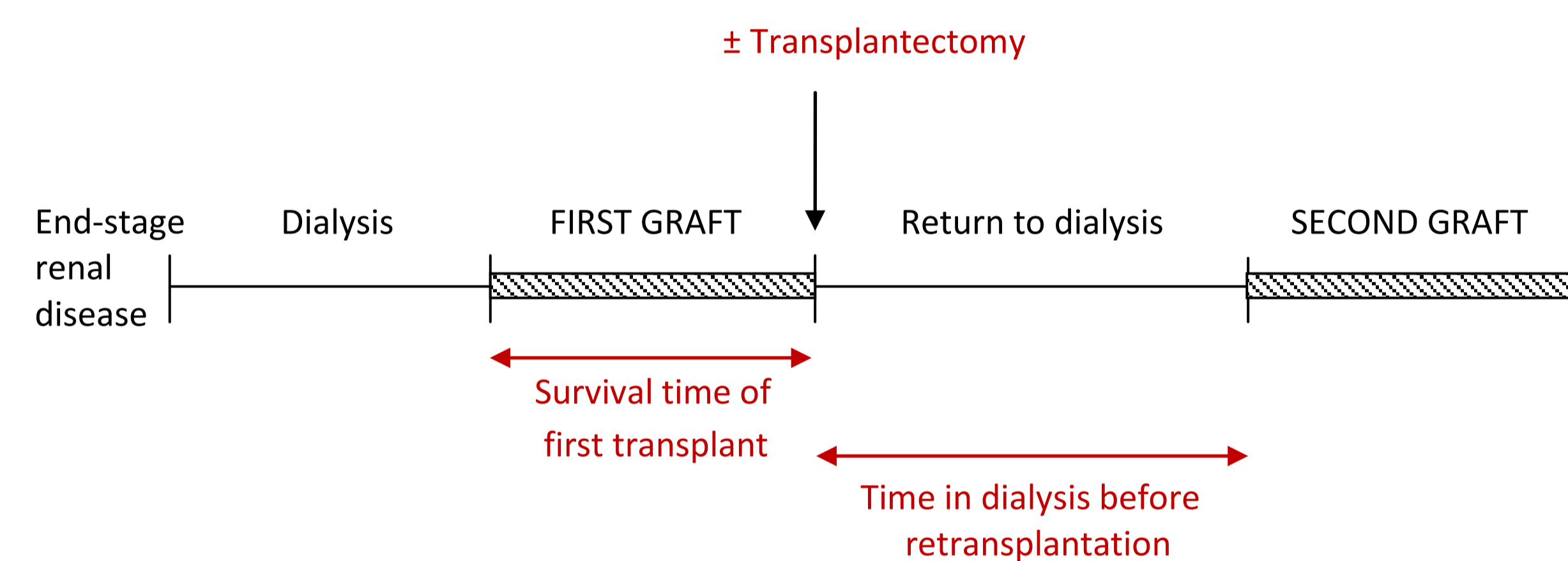


Figure : Clinical trajectory before second graft.

- ▶ Andersen et al. [1] proposed for this purpose a multiplicative model for relative survival based on expected mortality rates, using life tables.
- ▶ But the applications to endpoints other than mortality, with a reference group without a life time, has never been explored.

## OBJECTIVE

- ▶ To evaluate **difference in risk factors associated with time to graft failure** between STR (specific group) and FTR (reference group).

## MATERIALS

- ▶ Patients were selected from the French DIVAT ([www.divat.fr/en](http://www.divat.fr/en)) multicentric prospective cohort.
  - ▶ Centers: Nantes, Necker, Nancy, Toulouse, Montpellier, Lyon
  - ▶ Adult recipients
  - ▶ Transplanted from 1996 to 2010
  - ▶ Under mycophenolate mofetil and steroids at transplantation
    - ▶ **566 STR (group of interest) and 2206 FTR (reference group)**

## METHODS

- ▶ The main endpoint was the **patient-and-graft survival**  
 Event of interest = time between transplantation and graft failure

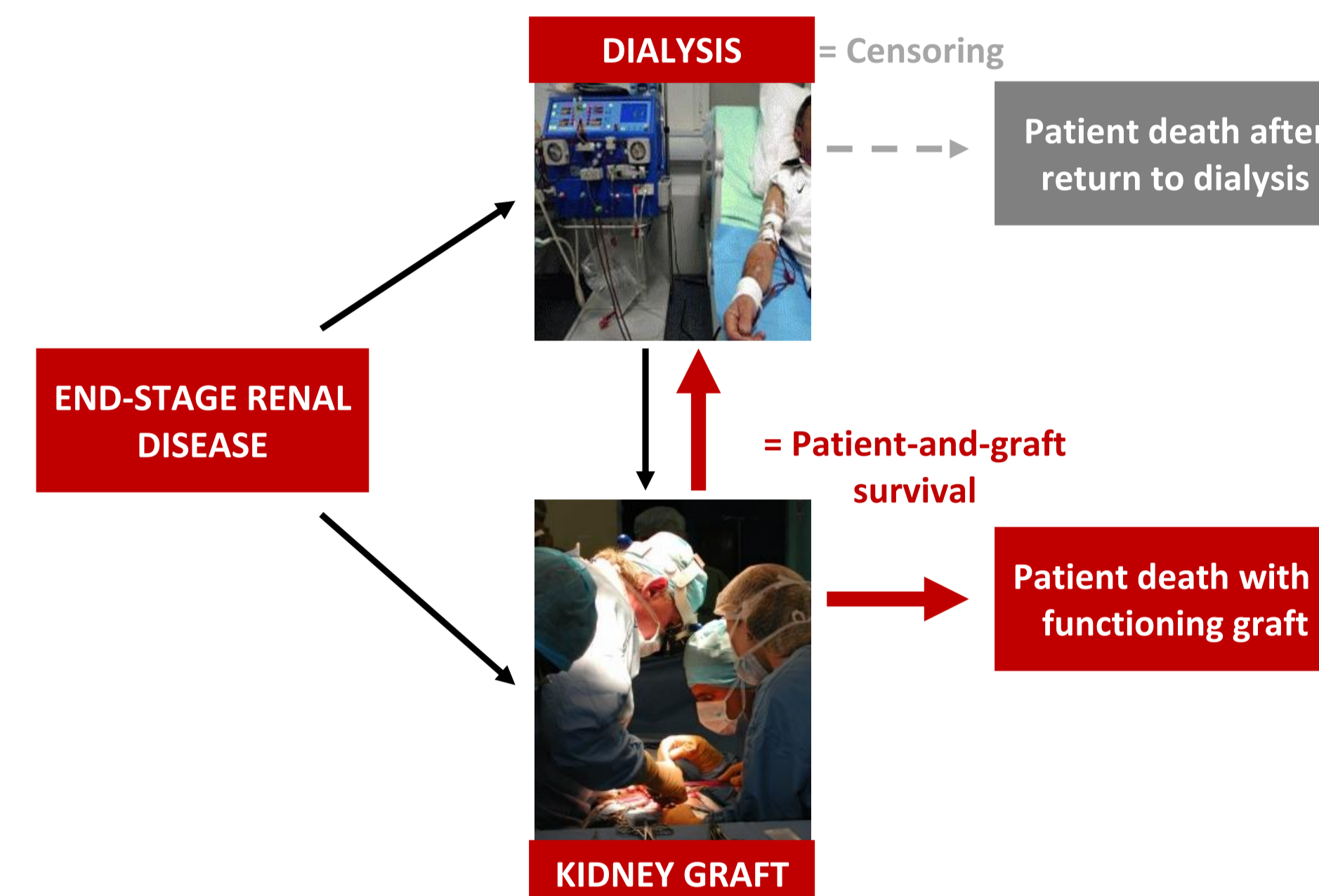


Figure : Definition of patient-and-graft survival.

- ▶ We developed a new multiplicative-regression model for relative survival [2, 1] applied to graft failure and with an expected hazard estimated from reference individuals (FTR) with similar characteristics to individuals of the relative group (STR).

## STUDY POPULATION

Table : Demographic characteristics at the date of transplantation

Demographic characteristics	FTR (N = 2206)		STR (N = 566)		p-value
	Number	(%)	Number	(%)	
Male recipient	1362	(61.7)	343	(60.6)	0.6536
Recipient $\geq 55$ years of age	994	(45.1)	181	(32.0)	<0.0001
Donor $\geq 55$ years of age	973	(44.1)	199	(35.2)	0.0002
Recipient BMI $\geq 30$ kg.m <sup>-2</sup>	235	(10.7)	28	(4.9)	<0.0001
History of diabetes	306	(11.0)	37	(6.5)	0.0002
HLA-A-B-DR incompatibilities $> 4$	326	(14.8)	39	(6.9)	<0.0001
Potentially recurrent causal nephropathy	666	(30.2)	240	(42.4)	<0.0001
History of cardiac disease	686	(31.1)	217	(38.3)	0.0012
History of malignancy	147	(6.7)	81	(14.3)	<0.0001
History of hepatitis B or C	96	(4.4)	72	(12.7)	<0.0001
Cold ischemia time $\geq 24$ h	552	(25.0)	202	(35.7)	<0.0001
Positive anti-class I PRA	355	(16.1)	351	(62.0)	<0.0001
Positive anti-class II PRA	319	(14.5)	414	(73.1)	<0.0001
Lymphocyte-depleting induction therapy	793	(35.9)	430	(76.0)	<0.0001
First graft survival $< 1$ year	-	-	131	(24.1)	-
Time before retransplantation $\geq 3$ years	-	-	272	(49.8)	-
Transplantectomy of the first graft	-	-	220	(38.9)	-

BMI, body mass index; PRA, panel reactive antibody; HLA, human leukocyte antigen

## RESULTS

- ▶ Donor gender and waiting time before re-transplantation were not taken into account in the expected hazards:
  - ▶ The risk of graft failure was **1.5-fold higher** for STR with grafts from males compared to STR with grafts from females ( $p = 0.0320$ ).
  - ▶ The risk of graft failure was **1.9-fold higher** for STR with a long waiting time compared to STR with a short waiting time ( $p < 0.0001$ ).
- ▶ Regarding the hazard ratios (HR) observed in FTR, expected HR associated with recipient and donor age would be respectively 1.39 and 1.34 in the STR. In fact, both variables appeared to be differently associated with the risk of graft failure between STR and FTR:
  - ▶ The HR associated with recipient age  $\geq 55$  years was **1.6-fold higher** for STR compared to FTR ( $p = 0.0480$ ).
  - ▶ The HR associated with donor age  $\geq 55$  years was nearly **2-fold lower** for STR compared to FTR ( $p = 0.0440$ ).

Table : Results of the relative survival model.

	Cox model (FTR)	Relative model (STR)	
	Expected HR	HR [95% CI]	p-value
Transplantation $< 2005$	1.33	0.97 [0.55-1.74]	0.9360
Male recipient	1.17	0.61 [0.38-1.05]	0.0720
Recipient age $\geq 55$ years	1.39	<b>1.65</b> [1.01-2.72]	0.0480
Donor age $\geq 55$ years	1.34	<b>0.59</b> [0.33-0.99]	0.0440
Male donor	-	<b>1.53</b> [1.03-2.48]	0.0320
Waiting time $> 3$ years	-	<b>1.92</b> [1.22-3.00]	<0.0001

## CONCLUSION

- ▶ **The adverse effect of recipient age was enhanced for STR**
  - ▶ A cumulative effect of the risk factors for STR (immunosuppression)
  - ▶ Clinicians should pay particular attention to recipient age for STR
- ▶ **The adverse effect of older transplants was attenuated for STR**
  - ▶ An indication bias with only high-quality donors proposed to STR?
  - ▶ A higher pre-graft non-HLA immunization, explaining why graft failure is due to immunological phenomena rather than transplant quality?

## REFERENCES

- [1] PK Andersen, K Borch-Johnsen, T Deckert, A Green, P Hougaard, N Keiding, and S. Kreiner. A cox regression model for the relative mortality and its application to diabetes mellitus survival data. *Biometrics*, 41(4):921-932, Dec 1985.
- [2] JD. Buckley. Additive and multiplicative models for relative survival rates. *Biometrics*, 40(1):51-62, Mar 1984.